REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-4 and 6 are pending. Claim 5 was previously canceled.

The amendments are supported by the original disclosure and, thus, no new matter has been added. If the Examiner should disagree, however, he is respectfully requested to point out the challenged limitation with particularity in the next Action so support may be cited in response. Amendments to claims 1 and 6 clarify that screening (not treatment) is the objection of the claimed invention. The antecedent basis of claims 2-4 has been corrected to conform with U.S. practice.

Entry of the amendments is requested to address the Examiner's objection on pages 2-3 of the Office Action and to correct informalities. Amendment of the claims will reduce the issues on appeal.

35 U.S.C. 112 – Enablement

Claims 1-4 and 6 were rejected under Section 112, first paragraph, because it was alleged that the specification does not reasonably provide enablement for methods of directly treating disease. Applicants traverse.

It has been proposed to amend claims 1 and 6 to recite the <u>way</u> in which agents identified by screening act with respect to the Smads and the TGF- or activin-inducible DNA element (i.e., the CAGA portion of a suitable promoter). This avoids the problems that the Examiner raises with respect to predicting activity *in vivo*. In fact on page 3 of the Office Action mailed April 24, 2001, the Examiner admitted that the specification is enabling for a method of screening agents associated with Smad3/4 (and, presumably Smad2 spliced in exon 3) and TGFβ by detecting the activity of said agent with such Smads and a CAGAC-containing oligo sequence derived from a TGFβ- or activin-inducible promoter.

Furthermore, regarding the allegation in the present Office Action that the claims read on to a method of therapy, it is hard to see how this can be concluded. The claims <u>clearly</u> recite a <u>Method of Screening</u>. Applicants' invention is a tool for identifying useful

agents, it does not purport to read on a method of treatment/therapy using the agent thus identified.

Withdrawal of the Section 112, first paragraph, rejection is requested because undue experimentation is not required to practice the claimed invention.

35 U.S.C. 103 – Nonobviousness

Claims 1-4 and 6 were rejected under Section 103(a) as allegedly unpatentable over Yingling et al. Applicants traverse because the cited reference clearly teaches away from the claimed method of screening. The technical arguments made on July 24, 2001 are reiterated and incorporated by reference herein to preserve them for appeal. Reconsideration is requested.

This is an improper rejection because the Patent Office's burden of establishing a *prima facie* case of obviousness has not been satisfied. It was admitted in the Office Action mailed April 9, 2002 that what was taught in the reference opposes the result taught by Applicants ("the disclosure as taught by Yingling et al. does describe a result that opposes that taught by the instant application"). Therefore, Yingling et al. cannot serve as the basis for an obviousness rejection of the claimed invention nor does it show a reasonable expectation of success.

The cited reference investigated the effect on TGFβ-inducible transcription of Smad protein binding to its DNA element. Yingling et al. failed to find such an effect. They taught, "mutations which eliminate the Smad DNA binding site do not interfere with . . . TGF-β-dependent transcriptional activation" (Abstract). The Examiner also admits on page 4 of this Office Action that Yingling et al. do not disclose a method of screening for an agent. Therefore, one of ordinary skill in the art would not have been motivated to modify the reference's binding assay because Yingling et al. did not teach that such agents would modulate transcription. No reasonable expectation of success was shown because Yingling et al. did not teach that modulating binding of a Smad protein to its DNA element would have a utility (cf. affecting TGFβ-inducible transcription).

Applicants have shown that their CAGA box sequence confers TGFβ-mediated induction (i.e., TGFβ-dependent transcriptional activation) and that a mutation in the

CAGA box sequence is unable to confer such induction (see Figs. 1B-C). In contrast, Yingling et al. speculate that the ability of Smad3/4 to directly bind DNA may have physiological relevance in regulating transcription of TGFβ-responsive genes but this at best, merely an invitation to experiment because of their own very clear findings to the contrary. Therefore, Yingling et al. would not have motivated one of ordinary skill in the art to modify the reference's binding assay or a reasonable expectation of success to do so because the failure of Yingling et al. to show that the CAGA box sequence confers TGFβ-inducible transcription clearly does not suggest practicing a method of screening agents that modulate such transcriptional activity or binding.

For a proper obviousness rejection under Section 103(a), the Examiner has the burden of establishing *prima facie* with evidence or reasons that, i*nter alia,* at the time of the invention, (1) the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed method and (2) the prior art would also have revealed that in so carrying out, those of ordinary skill would have a reasonable expectation of success. See *In re Vaeck,* 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure. *Id.*

Applying the two-prong test set forth in *Vaeck*, it is apparent that the Examiner has not established a *prima facie* case of obviousness. First, there is no suggestion in Yingling et al. that mutations in the Smad binding sites interfere with TGFβ-dependent transcriptional activation. In fact, Yingling et al. teach just the opposite. Second, Yingling et al. suggest that the Smad DNA binding site is not essential for TGFβ transcriptional activation. Therefore, the cited reference does not show a reasonable expectation of success. If one of ordinary skill in the art reads the Yingling et al. reference, that person would not have been motivated to modify the reference's binding assay to produce the claimed method of screening since, if Smad binding according to Yingling et al. was not essential for TGFβ activation, then this would not be a useful therapeutic intervention point. Hence, there would be no point in setting up a screen to identify agents interfering with this binding because such agents would not modulate TGFβ-inducible transcription

according to Yingling et al. Therefore, Applicants' claims are patentable because they are nonobvious.

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to a person of ordinary skill in the art at the time it was made.

Conclusion

Having fully responded to all of the pending objections and rejections contained in the Office Action (Paper No. 19), Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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APPENDIX
MARKED-UP VERSION TO SHOW CHANGES

IN THE TITLE

The title is amended as follows: METHOD OF SCREENING [THERAPEUTIC] AGENTS

IN THE CLAIMS

The claims are amended as follows.

1. (2x Amended) A method for screening [therapeutic] agents [for use in combating fibrotic disorders, abnormal wound healing, abnormal bone formation, cancer development, hematopoiesis, neuroprotection and immune and inflammatory disorders where associated with gene regulation by] that modulate transcriptional activity or binding of at least one [or more] Smad protein[s] selected from the group consisting of: Smad2 spliced in exon 3, Smad3, and Smad 4 [and] with a DNA element selected from the group consisting of: a TGFβ-inducible DNA element [or] and an activin-inducible DNA element, said method comprising detecting or assaying the extent or result of transcriptional activity or binding in the presence of said agent between said at least one [an] Smad protein or a DNA binding fragment thereof and a double strand oligonucleotide comprising the sequence 5' WXYCAGACZ 3' or a functional equivalent thereof, wherein in said nucleotide sequence, W represents A or G, X represents G or T, Y represents C, A, G or T and Z represents A or C.

2. (Amended) [A] The method according to claim 1 wherein the double strand oligonucleotide comprises the sequence 5' WXYCAGACZ 3' or a functional equivalent thereof, wherein in said oligonucleotide sequence W represents A or G, X represents G or T, Y represents C, A or G and Z represents A or C.

3. (Amended) [A] The method according to claim 1 or 2 wherein the double strand oligonucleotide comprises the sequence 5' AG(C/A)CAGACA 3',or a functional equivalent thereof.

4. (Amended) [A] The method according to claim 1 or 2 wherein the double strand oligonucleotide comprises the sequence 5' ATGCAGACA 3' or 5' GGCCAGACA 3', or a functional equivalent thereof.

6. (2x Amended) A kit for screening agents [for combating fibrotic disorders, abnormal wound healing, abnormal bone formation, cancer development, hematopoiesis, neuroprotection and immune and Inflammatory disorders where associated with gene regulation by] that modulate transcriptional activity or binding of at least one [or more] Smad protein[s] selected from the group consisting of: Smad2 spliced in exon 3, Smad3, and Smad 4 [and] with a DNA element selected from the group consisting of: a TGFβ-inducible DNA element [or] and an activin-inducible DNA element, said kit comprising: [.]

- said at least one [a] Smad protein;
- TGFβ or activin; and
- a double strand DNA molecule comprising the sequence 5' WXYCAGACZ 3' or a functional equivalent thereof, wherein in said nucleotide sequence, W represents A or G, X represents G or T, Y represents C, A, G or T and Z represents A or C.